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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/767,041	01/22/2001	Hilda E. Smith	4726US	3344

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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	**PAPER NUMBER**
1645	21

DATE MAILED: 01/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/767,041	SMITH, HILDA E.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2002 and 06 May 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-25 and 31-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-25 and 31-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3 separate*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-14 and 26-30 have been cancelled. Claims 12-25 and 31-51 are pending and under examination.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on two different applications filed in EP on July 22, 1998. It is noted, however, that applicant has not filed a certified copy of the EP 98202456.5 and 98202467.1 applications as required by 35 U.S.C. 119(b).

Drawings

The drawings in this application are approved by the Draftsperson.

Specification

The disclosure is objected to because of the following informalities: the substitute specification filed 1/22/01 is not acceptable. It does not contain the entire disclosure of the original specification and the marked up copy does not include cancellation of pages. For example, pages 62-193 are missing from the clean copy and Table 9 is present at page 61 in the clean copy and at page 62 on the marked up copy and the internal sequence listing is not present. As such, the marked up copy does not correspond to the clean copy. Further, neither correspond to the originally filed specification. Additionally, the amendments to the specification as recited in the preliminary amendment filed with this application could not be entered because the corresponding page and line number can not be found in the substitute specification filed 1/22/01 and they are too numerous to be legibility entered. A substitute specification including all preliminary amendments and amendments to the claims is required pursuant to 37 CFR 1.125(a) for reasons set forth

herein. A substitute specification filed under 37 CFR 1.125(a) must only contain subject matter from the original specification and any previously entered amendment under 37 CFR 1.121. If the substitute specification contains additional subject matter not of record, the substitute specification must be filed under 37 CFR 1.125(b) and (c). Should Applicants wish to cancel the internal sequence listing and/or the list of references, the marked up copy should include indication of cancellation of these portions.

Additionally, the disclosure is objected to at page 34 [0132] because the description references descriptive matter that is not contained in the recited Tables 1 and Table 3. Correction is required. Applicants are specifically cautioned against adding new matter to the specification as filed.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not identify one of the foreign applications for patent or inventor's certificate on which priority is claimed pursuant to 37 CFR 1.55, and any foreign application having a filing date before that of the application on which priority is claimed, by specifying the application number, country, day, month and year of its filing. It is noted that EP 98202467.1 for which Applicants claim priority in the first line of the specification is not recited in the oath/declaration. Applicant has not complied with the requirements of 37 CFR 1.63(c), since the oath, declaration or application data sheet does not acknowledge the filing of this foreign application. A new oath, declaration or application data sheet is required in the body of which the present application should be identified by application number and filing date.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892 or on the 1449's, they have not been considered.

The information disclosure statements filed 1-22-01, 5-6-03 and 5-19-03 have been considered with the exception of EP 0 750 043 A1, which fails to comply with either 37 C.F.R. 1.98 (3) (i) or (3) (ii). Further, it is noted that the publication date and name of applicant for WO 92/21465 has been corrected to accurately reflect the cited WO document.

Initialed copies of the information disclosure statements are enclosed.

Election/Restrictions

The election/restriction is moot in view of the cancellation of the non-elected claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-25 and 31-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to mutants of *Streptococcus suis* having a modified capsular gene cluster or a recombinant microorganism comprising at least a part of a capsular gene cluster of *Streptococcus suis*, wherein the gene cluster comprises a deletion, insertion or (point)-mutation. The claims lack any specific nucleic acid structure of any capsular gene cluster or mutant thereof. The specification at paragraph [0161] teaches that there are at least 35 different capsular serotypes of Streptococcus suis. The specification teaches a complete nucleic acid sequence for serotype 2 and partial sequences for serotypes 1, 7 and 9. The specification teaches specific mutations of serotype 2 cpsB and cps E/F genes. The specification does not place any structure, chemical or functional limitations on the variants of capsular gene cluster or any structure on the cluster per se. The recitation of "capsular gene cluster" or "a capsular gene cluster of Streptococcus suis gene cluster" does not convey a common structure or function. The scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Although the specification teaches that variants can be readily screened, the specification and the claim do not provide any guidance on the structure of the polypeptide and what changes can or can not be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure and the claims. No common structural attributes identify the members of the genus. The general knowledge

and level of skill in the art do not supplement the omitted description, because specific, not general guidance is needed. Since the disclosure fails to describe the common attributes or structural characteristics that identify members of the genus, and because the mutant genus is highly variant, the function of "capsular" alone is insufficient to describe the genus of gene clusters. One of skill in the art would reasonable conclude that the disclosure, fails to provide a representative number of species when the claims provide no structure to describe the claimed genus. Applicants were not in possession of the claimed genus because the specification does not convey to one of skill in the art a representative number of variants in structure and function and does not set forth any structure in the claims. The genus of gene clusters with the claimed "capsular" function is substantial and highly variant because the nucleic acids do not have a commonly claimed structure and function. The recitation of "capsular gene cluster" does not convey a common structure nor a common function. As such, generic sequences that are unrelated via structure and function are highly variant and not conveyed by way of written description by the specification at the time of filing. As such the specification lacks written description for the highly variant genus of mutants and gene clusters and one skilled in the art would not recognize that applicants had possession of the genus of claimed mutants of capsular gene clusters.

Claims 15-25 and 31-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to recombinant *Streptococcus suis* mutants having a modified capsular gene cluster, a recombinant microorganism comprising at least a part of a capsular gene cluster of *Streptococcus suis* wherein the gene cluster comprises a deletion,

insertion or point mutation and vaccines comprising *Streptococcus suis* mutant having a modified capsular gene cluster or vaccines comprising a recombinant microorganism comprising at least a part of a capsular gene cluster of *Streptococcus suis* and variations thereof.

The teachings of the specification are limited to descriptions of part of the capsular gene cluster for serotypes 2, 1, 9 and 7 of *Streptococcus suis* and specific substitutions of the cps2B and cps2E/F genes with a spectinomycin-resistance gene. The specification teaches that the specific modification of the serotype two cpsB and cpsE/F genes provide for a *Streptococcus suis* strain with deficient capsular production that is efficiently phagocytosed and killed by phagocytes (see specification [0130-0131]). The specification directs one of skill in the art to the use of the claimed recombinant microorganisms as vaccines. The specification is not enabled for using the mutant or recombinant microorganisms as vaccines for the following reasons. The specification, as filed, fails to teach any other use of the mutant *Streptococcus suis* or recombinant microorganism that comprises at least a part of a capsular gene cluster that has a deletion insertion or point mutation. The dictionary definition of vaccine is "A prophylactic or therapeutic material containing antigens derived from one or more pathogenic organisms which, on administration to man or animal, will stimulate active immunity and protect against infection with these or related organism (i.e. produce protective immunity)." (The Dictionary of Immunology, Herbert et al eds, Academic Press, 1995) would clearly realize the critical deficiency of this specification with respect to vaccines. There is absolutely no demonstration of protective immunity upon administration in any animal model of disease. Such is required by the common meaning as demonstrated by the dictionary definition and is reiterated in Plotkin et al that teaches that it is well recognized in the vaccine art, that it is unclear whether an antigen(s) derived from a pathogen will elicit protective immunity. Ellis, R.W. (Chapter 29 of "VACCINES" [Plotkin, S.A. et al. (eds) published by W. B. Saunders company (Philadelphia) in 1988, especially page 571, 2nd full

paragraph] exemplifies this problem in the recitation that "The key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.... and thus protect the host against attack by the pathogen". The teachings of the specification are devoid of any teaching that animals in a normal infection generate antibodies that bind the microorganism or heterologous polypeptide(s) produced therefrom (i.e. as it relates to claims 24, 25, and 41-51) as claimed and therefore is not clear that the heterologous polypeptides of the invention are capable of generating an antibody response during a normal course of infection with *Streptococcus suis*. Further, mere production of a heterologous polypeptide does not necessarily provide to access of the immune system to the polypeptide. For example, internal mutant enzymes would not be expected to be adequately presented to the host immune system for generation of a specific response and the art of record teaches that specification fails to teach that any immune response generated upon injection by the claimed recombinant microorganisms to the heterologous non-*Streptococcal* pathogenic protein provide for a protection against infection of the pathogen. Vaccines by definition trigger an immunoprotective response in the host vaccinated and mere antigenic response is insufficient. The specification fails to teach even one of the claimed heterologously produce polypeptides in any recombinant Streptococcus or recombinant microorganism comprising at least a part of the capsular gene cluster alone or in combination with other antigens does in fact confer protection from infection, as is requisite of a vaccine composition. Further, as to claim 16 and every claim dependent thereon, since the gene cluster comprises a mutation (insertion, deletion or point) and since the capsular structures of *Streptococcus suis* and other organisms are defined by the particular function of the genes to arrive at different chemical structures, it is not readily apparent that any mutation in the "at least a part of a capsular gene cluster of *Streptococcus suis*" when present in a recombinant microorganism is capable of producing the appropriate *Streptococcus suis* capsular serotype effective for immune

response and protection from infection. Therefore, the recombinant microorganisms of claims 16 and 17 are would be ineffective in producing a *Streptococcus suis* serotype and are therefore ineffective at functioning as a vaccine for infection by *Streptococcus suis*. As such, the specification completely fails to teach how to use such recombinant mutants. The courts have held that it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. (Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001). Moreover, the specification must have been enabling at the time the invention was made and developments after the time of filing are of no consequence to what one skilled in the art would have believed at the time of filing (*In re Wright*, 27 USPQ2d 1510). In the absence of a teaching of the claimed recombinant Streptococcus mutants or recombinant microorganisms comprising at least a part of a mutant gene cluster are effective in prevention of any disease, the specification is not be enabled for vaccines or has any other disclosed use for the mutants as claimed. In view of the unpredictability of the art, the lack of teachings of the specification, it would require undue experimentation on the part of the skilled artisan to use the invention as claimed.

Claims 16, 17, 31 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claim 16, the claim recites the phrase "(point)-mutation" and it is unclear what the function of the parenthesis around "(point)" represent. Is this phrase intended to specifically modify "mutation" or is it a merely and exemplification of a type of mutation possible and non-limiting. Clarification is respectfully requested.

As to claim 17, the recitation of "wherein said microorganism comprises a lactic acid bacterium" is confusing because it is unclear if the recombinant microorganism is in fact a lactic acid bacterium or is something else such as a population of recombinant

microorganisms, one of which may be a lactic acid bacterium. This issue may be resolved by amending the claim to recite --..wherein the microorganism is a lactic acid bacterium.--

Claim Rejections - 35 USC § 102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 15, 16, 17, 18, 19, 20, 21, 22, 23, 31, 32, 33, 34, 35, 36, 37, 38, 39 and 40 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Smith et al (Infection and Immunity, 67(4):1750-1756, April 1999, of record on 1449).

Smith et al teach two non-encapsulated isogenic mutants in the cps2B and cps2EF genes of Streptococcus suis. As such, the mutants of the prior art anticipated the claimed invention at it was "by another" and the claim for foreign priority has not been perfected. The properties of capable of survival in an immune-competent host are inherent properties of the capsule-deficient mutants. The recitation of "vaccine" is an intended use of the product and does not distinguish the product of the prior art from the product as claimed. Charland et al therefore anticipates claims 15, 16, 17, 18, 19, 20, 21, 22, 23, 31, 32, 33, 34, 35, 36, 37, 38, 39 and 40.

Claims 15, 16, 17, 18, 19, 20, 21, 22, 23, 31, 32, 33, 34, 35, 36, 37, 38, 39 and 40 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Charland et al (Microbiology, 144:325-332, February 1998, of record on 1449).

Charland et al two *Streptococcus suis* serotype 2 mutants deficient in capsular expression wherein the mutants are derived by transposition TN916 insertion (see page 326, column 1 in Methods). Both mutants were biochemically identical to the wild-type strain and the production of other putative virulence factors of *S. suis* such as haemolysin, MRP and EF was not affected by transposition (page 327, paragraph bridging columns 1-2). The properties of capable of survival in an immune-competent host are inherent properties of the capsule-deficient mutants. The recitation of "vaccine" is an intended use of the product and does not distinguish the product of the prior art from the product as claimed. Charland et al therefore anticipates claims 15, 16, 17, 18, 19, 20, 21, 22, 23, 31, 32, 33, 34, 35, 36, 37, 38, 39 and 40.

Claims 16, 17, 31 and 34 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Yother et al (WO 95/31548, published 23 November 1995, of record on 1449).

Yother et al teach the capsular polysaccharide genes and flanking regions of *Streptococcus pneumoniae*. Yother teach the expression of the capsular gene produces in a recominant host cell defined as a *Bacillus*, *Stphylococcus*, *Streptococcus* or *Streptococcus pneumoniae* host cell. The recombinant cells of Yother et al possess at least a part of a gene cluster of Streptococcus suis in that they have a single amino acid in common and have a different gene organization. In view that that there is no structural or chemical characterization of the capsular gene cluster, that the gene cluster of the prior art posses at least a part of the gene cluster of *Streptococcus suis* (i.e. a single amino acid) and that the gene cluster of the art is apparently structurally different (i.e.

has one or more deletions, insertions or point mutations), Yother et al anticipates the instantly claimed invention.

Citation of Relevant Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Gottschalk et al (Journal of Clinical Microbiology, 37(12):4242, December 1999) teach that experimental infection models for *S. suis* can be mesleading. The pig and mouse models sometimes correllate well and in other cases not at all. Additionally, the art teaches that since results from experimental infections of *S. suis* in swine may rely upon the immunological status of the animals, the route of infection, the size of the inoculumand the presence of *S. suis* as a normal inhabinant of the upper respiratory tract, caution should be exercised wtih the terms virulent and avirulent are used to reach definitive conclusions.

Segura et al (FEMS Immunology and Medical Microbiology 12:189-195, 1998) teach singificant functional and biological differences between grop B *Streptococcus* and *S. suis.* In particular, the properties of the ability of the microorganism to be phagocytosed and killed is different between these two microorganisms. The physiological behavior of one (i.e. ability to be phogocytosed and killed by leukocytes) does not predict the physiological behavior of the other.

Reams et al (J Vet. Diagn Invest 8:119-121, 1996) teach that multiple serotypes and strains of *Sterptococcus suis* exist in naturally infected swine herds.

Staats et al (Veterinary Research Communications, 21:381-407, 1997) provides fo the state of the art with *Streptococcus suis.*

Brazeau et al, (Microbiology, 142:1231-1237, 1996) provides for analysis of survival of S. suis capsular type 2 inside of murine macrophages. The study indicated that both

capsulated virulent and non-virulent strains were readily encapsulated but only the virulent strains survived inside the phagosome for at least three hours.

Status of the Claims

All claims stand rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 703-305-7555. After January 27, 2004 the examiner can be reached at telephone number 571-272-0855 The examiner can normally be reached on M-F 9:30pm-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Smith Lynette can be reached on before January 27, 2004 at 703-308-3909, after January 27, 2004 at 571-272-0864. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Patricia A. Duffy, Ph.D.
Primary Examiner
Art Unit 1645